

Docket No. 53001AUSM1

REMARKS**Status of Claims and Claim Amendments**

Claims 1-22 were pending in the application. Claims 1-7 and 20-22 are canceled, in view of a restriction requirement, without prejudice to filing the subject matter of the claims in a continuing application. Claims 8-10, 15-17 and 19 are canceled, without prejudice to filing the subject matter therein in a continuing application. New claims 23-25 have been added. The claims now remaining in the application are claims 11-14, 18 and 23-25.

Claim 11 is amended to rewrite the claim in independent form and also to remove subject matter related to a non-elected invention, without prejudice to claiming such subject matter in a continuing application. Certain of the other claims have been amended to correct certain inadvertent typographical errors, formatting, and the like. All amendments to the claims, as well as new claims 23-25, are supported by the specification as filed, so that no new matter has been added.

Rejection under 35 U.S.C. §112, 2nd paragraph

Claims 8-16 have been rejected as being indefinite because the term "substituted" renders the claims in which it appears indefinite where the particular substituent moieties are not identified.

Response: The rejection is respectfully traversed. The test for definiteness is whether one of ordinary skill in the art would understand the bounds of the claim when read in light of the specification. If the claims, read in light of the specification, reasonably apprise those skilled in the art of the scope of the invention, §112 demands no more (*Miles Laboratories, Inc. v. Shandon Inc.*, 27 USPQ2d 1123 (Fed. Cir. 1993), *cert. denied*, 510 U.S. 1100 (1994)).

Firstly, certain of the rejected claims do not in fact include the term "substituted" at all or, if present, it is included together with the particular substituent moieties. Thus, claims 13 and 14 should not be included in this rejection, and it is requested that the rejection be withdrawn as it pertains to these claims.

Further, in the present case, Applicants intend to claim any substituent moiety. This may indeed be broad, but it is well-established that breadth is not tantamount to indefiniteness. The specification specifically discloses many moieties that would be appropriate as substituents on the various chemical groups claimed. See, e.g., substituents for alkyl at page 35, lines 20-22; for cycloalkyl at page 35, lines 28-30; for amino at page 35, line 33 to page 36, line 3; for aryl at page 36, lines 13-15; and for heterocyclyl at page 37, lines 25-28. Additionally, compounds with various substituents are exemplified throughout the specification. Thus, one of skill in the art would, in light of the specification and of the general knowledge in the field, know what is meant by the term "substituted" and would understand the scope of the claims.

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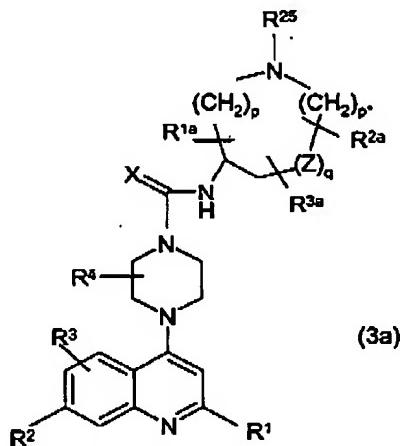
In view of the above, it is believed that all of the claims are definite, and it is requested that this rejection be withdrawn.

Rejections under 35 U.S.C. §102(b)

1. Claims 8-19 are rejected as being anticipated by Matsuno et al., U.S. Patent 6,773,896 (US '896).

Response: This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration (*W.L. Gore & Associates v. Garlock, Inc.*, 220 USPQ 303, at 313 (Fed. Cir. 1983); emphasis added). There must be no difference between the claimed invention and the reference disclosure (*Scripps Clinic & Research Foundation v. Genentech Inc.*, 18 USPQ 2d 1001, at 1010 (Fed. Cir. 1991); emphasis added).

The present invention is directed to substituted quinolines of formula 3a.



The Matsuno et al. reference, in contrast, does not disclose compounds having a Z substituent, an R²⁵ substituent or an R^{1a} substituent, to name just a few differences between the two disclosures. Therefore, Matsuno et al. cannot anticipate the claimed invention, and it is requested that this rejection be withdrawn.

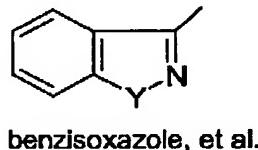
2. Claims 8-19 are rejected as being anticipated by O'Malley et al., U.S. Patent 5,494,908 (US '908).

Response: This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the

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disclosure in a single prior art reference of each element of the claim under consideration; there must be no difference between the claimed invention and the reference disclosure.

The present invention is directed to substituted quinolines of formula 3a. The O'Malley et al. reference discloses only substituted benzisoxazoles, benzpyrazoles and benzisothiazoles (Y = O, N and S, respectively).

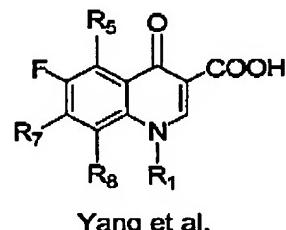
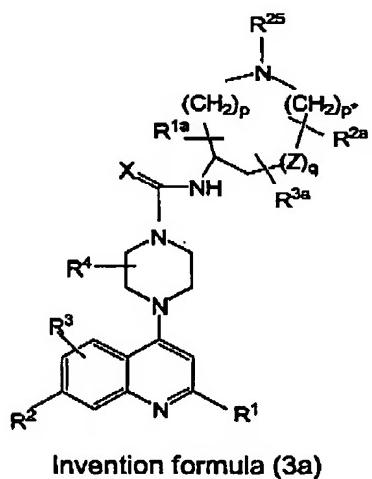


Quinolines are nowhere disclosed in O'Malley '908. Therefore, O'Malley et al. cannot anticipate the claimed invention, and it is requested that this rejection be withdrawn.

3. Claims 8-17 are rejected as being anticipated by Yang et al., CN 1234397 (CN '397).

Response: This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration; there must be no difference between the claimed invention and the reference disclosure.

The present invention is directed to substituted quinolines of formula (3a). The Yang et al. reference discloses carbostyryl compounds having *required* structural differences from the compounds of the present invention, most notably at position 3 (COOH in Yang vs. H in present invention), position 4 (oxo vs. substituted piperazine) and position 7 (piperazine vs. halogen) of the quinoline.



Therefore, Yang et al. cannot anticipate the claimed invention, and it is requested that this rejection be withdrawn.

4. Claims 8-19 are rejected as being anticipated by Matsuno et al., EP 8882 717.

Response: This rejection is respectfully traversed, for the reasons stated in 1. above. This Matsuno EP application is the corresponding equivalent to U.S. Pat. 6,773,896, and the comments regarding USP '896 apply to this EP reference and this rejection as well.

5. Claim 8-19 are rejected as being anticipated by Rhone Poulenc, FR 84 902 (FR '902).

Response: This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration; there must be no difference between the claimed invention and the reference disclosure.

The present invention is directed to substituted quinolines of formula 3a. FR '902, In contrast, discloses only simple piperazinylquinoline derivatives; it does not disclose the heterocycl-NH-C(=X)-piperazinylquinoline compounds of the present invention. Therefore, FR'902 cannot anticipate the claimed invention, and it is requested that this rejection be withdrawn.

6. Claim 8-19 are rejected as being anticipated by Agrawal et al., *Indian J of Chem* 1987.

Response: This rejection is respectfully traversed. It is believed that the Patent Office has not met its burden of establishing a *prima facie* case of anticipation. Anticipation requires the disclosure in a single prior art reference of each element of the claim under consideration; there must be no difference between the claimed invention and the reference disclosure.

The present invention is directed to substituted quinolines of formula 3a. Agrawal, In contrast, discloses only simple piperazinylquinoline derivatives (see, pp 551-552); it does not disclose the heterocycl-NH-C(=X)-piperazinylquinoline compounds of the present invention. Therefore, Agrawal et al. cannot anticipate the claimed invention, and it is requested that this rejection be withdrawn.

Rejections under 35 U.S.C. §103(a)

1. Claims 8-19 are rejected as being unpatentable over Matsuno et al., U.S. Patent 6,169,088 (US '088). In particular, the Office Action states that

Matsuno teaches a generic group of quinoline derivatives, which embraces Applicants' claimed compounds. (See formula 1, col. 2 and definitions for V, W, X, Y, Z ...). One of

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ordinary skill in the art would have been motivated to select the claimed compounds from the genus in the reference since such compounds would have been suggested by the reference as a whole.

Response: Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

It is well-settled that in considering obviousness under 35 USC §103, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references which sets forth the necessary elements of the claimed invention *and* which provides the motivation for combining those elements to yield the claimed invention. See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

When, as here, there is only a single reference cited, the Federal Circuit has noted that "[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference" (*In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000); see also *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000)).

Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is *no* suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting the combination, the reference cited by the Examiner *fails* to set forth necessary elements of the claimed invention.

Contrary to the Office Action's statement, the quinoline derivatives of Matsuno et al. do not embrace Applicants' claimed compounds. As an example, Matsuno does not teach or suggest an oxo- or thioxo-substituted heterocycl-NH-C(=X)- group on the piperazinyl portion of a piperazinyl quinoline compound. Nor would it be obvious that such a substantial and non-obvious modification of the Matsuno compounds that are inhibitors of phosphorylation of platelet-derived growth factor receptor to hinder abnormal cell growth and cell wandering would give a different compound having CCR5 receptor antagonistic activity for treatment of inflammatory and autoimmune diseases.

The claimed quinoline structure of the present invention is neither taught nor suggested in Matsuno. Thus, there is no suggestion whatever to make any of the changes that are necessary to

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the Matsuno compounds to produce the presently claimed compounds, nor is there any motivation to make the modifications necessary to do so. Therefore, the claims are not obvious in view of Matuno et al.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

2. Claims 8-19 are rejected as being unpatentable over O'Malley et al., U.S. Patent 5,494,908 (US '908). In particular, the Office Action states that

O'Malley teaches a generic group of quinoline derivatives, which embraces Applicants' claimed compounds. (See formula 1, col. 6 and definitions for m, R¹-R⁶)....

Response: Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

It is well-settled that in considering obviousness under 35 USC §103, the prior art as a whole must be considered and its teachings must be viewed as they would have been by one of skill in the art at the time of the invention. To properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references which sets forth the necessary elements of the claimed invention *and* which provides the motivation for combining those elements to yield the claimed invention. See, e.g., *Northern Telecom Inc. v. Datapoint Corp.*, 15 USPQ2d 1321, 1323 (Fed. Cir. 1990). The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. *In re Grabiak*, 226 USPQ 870 (Fed. Cir. 1985). If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

When, as here, there is only a single reference cited, the Federal Circuit has noted that "[e]ven when obviousness is based on a single prior art reference, there must be a showing of a suggestion or motivation to modify the teachings of that reference" (*In re Kotzab*, 55 USPQ2d 1313, 1316-17 (Fed. Cir. 2000); see also *SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp.*, 55 USPQ2d 1927, 1931 (Fed. Cir. 2000)).

Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is *no* suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting the combination, the reference cited by the Examiner *fails* to set forth necessary elements of the claimed invention.

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Contrary to the Examiner's interpretation, the compounds disclosed by O'Malley et al. do not teach a generic group of quinoline derivatives. Quinolines, as claimed in the present invention, are 10-membered bicyclic heterocycles having one ring nitrogen atom and nine ring carbon atoms. O'Malley, in contrast, discloses benzisoxazoles, benzpyrazoles and benzisothiazoles, which are 9-membered bicyclic heterocycles having seven ring carbon atoms and two ring hetero atoms (N and O, N and N, and N and S, respectively). The quinoline compounds of the present invention are not in any way embraced by the compounds of O'Malley. Further, there is nothing in the reference that teaches or suggests to modify the compounds of O'Malley to give the compounds of the present invention. Firstly, the chemistry is substantially different and it would not be expected by those of skill in the art to modify the O'Malley compounds in at least two ways in order to obtain the presently claimed compounds. Nor would it be obvious that such a (non-obvious) modification of compounds having acetylcholinesterase inhibitory activity (for treatment of memory dysfunctions) and monoamine oxidase inhibitory activity (for use as antidepressants) would give a substantially structurally different compound having CCR5 receptor antagonistic activity (for treatment of inflammatory and autoimmune diseases). There is simply no motivation present in O'Malley to do so.

The claimed quinoline base structure of the present invention is neither taught nor suggested in O'Malley et al. Thus, there is no suggestion whatever that the quinoline group of the invention should be substituted for the heterocycles of O'Malley, and there is certainly no motivation to combine the teachings in O'Malley to get the quinoline group since, in fact, O'Malley does not in any way teach such a group. O'Malley et al. fail to set forth a necessary element, the quinoline group, of the claimed invention. Therefore, the claims are not obvious in view of O'Malley et al. US '908.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

3. Claims 8-19 are rejected as being unpatentable over Yang et al., CN 1234397 (CN '397). In particular, the Office Action states that

Yang teaches a generic group of quinoline derivatives, which embraces Applicants' claimed compounds. (See Abstract and formula 1, p. 1).... The claims differ from the reference by reciting specific species and a more limited genus than the reference. However, it would have been obvious ... to select *any of the species of the genus taught by the reference, including those instantly claimed*, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have ... the same use as taught for the genus as a whole. [emphasis added].

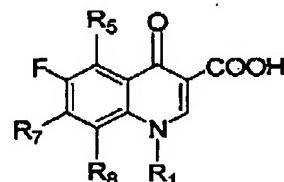
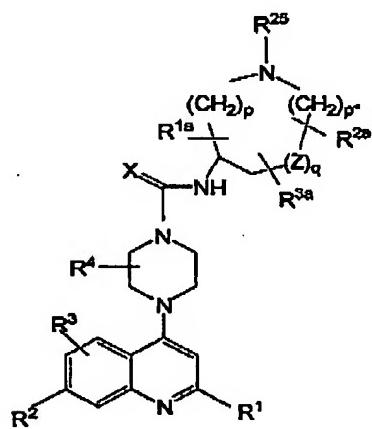
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Response: Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

As has been discussed more fully above, to properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references or, as in the present case to a single reference that sets forth the necessary elements of the claimed invention and which provides the motivation for combining those elements to yield the claimed invention. The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is *no* suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting the combination, the reference cited by the Examiner *fails* to set forth necessary elements of the claimed invention.

Contrary to the Office Action's statement, the quinoline derivatives of Yang do not embrace Applicants' claimed compounds. Again, the present invention is directed to substituted quinolines of formula (3a), whereas the Yang et al. reference discloses quinolines having *required* structural differences from those of the present invention, most notably at position 3 (COOH in Yang vs. H in present invention), position 4 (oxo vs. substituted piperazine) and position 7 (piperazine vs. halogen).



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Further, there is nothing in the reference that teaches or suggests to modify the compounds of Yang to give the compounds of the present invention. Firstly, the chemistry is substantially different and it would not be expected by those of skill in the art to modify the Yang compounds in at least four substantial ways in order to obtain the presently claimed compounds. First, the carboxyl group at position 3, which is required in Yang, must be removed. Second, the oxo at position 4, also required in Yang, must be removed. Third, the piperazinyl at position 7 must be relocated to position 4. Fourth, the piperazinyl must be substituted with an oxo- or thioxo-substituted heterocyclyl-NH-C(=X)-group, which complex group is nowhere taught in or suggested by Yang. In fact, not one of the above changes is in any way taught or suggested by Yang, let alone a combination of all of these changes.

Nor would it be obvious that such a substantial and (non-obvious) modification of carbostyryl compounds having anti-mycoplasma (mycoplasma are prokaryotic microorganisms) activity (that is, activity against microbes) would give a substantially structurally different compound having CCR5 receptor antagonistic activity for treatment of inflammatory and autoimmune diseases.

The claimed quinoline structure of the present invention is neither taught nor suggested in Yang. Thus, there is no suggestion whatever to make any, let alone all of the changes that are necessary to the Yang compounds to produce the presently claimed compounds, nor is there any motivation to make the modifications necessary to do so. Therefore, the claims are not obvious in view of Yang et al.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

4. Claim 8-19 are rejected as being unpatentable over Rhone Poulenc, FR 84 902 (FR '902). In particular, the Office Action states that

Poulenc teaches a generic group of quinoline derivatives, which embraces Applicants' claimed compounds. (See Abstract and formula 1, p. 1 and pp 1-3, 6-7 and definitions for A, R₁ and R₂). . . . The claims differ from the reference by reciting specific species and a more limited genus than the reference. However, it would have been obvious . . . to select *any of the species of the genus taught by the reference, including those instantly claimed*, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have . . . the same use as taught for the genus as a whole. [emphasis added]

Response: Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

As has been discussed more fully above, to properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references or, as in the present case to a single reference that sets forth the necessary elements of the claimed invention

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and which provides the motivation for combining those elements to yield the claimed invention. The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is *no* suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting the combination, the reference cited by the Examiner *fails* to set forth necessary elements of the claimed invention.

Contrary to the Office Action's statement, the quinoline derivatives of Poulenc do not embrace Applicants' claimed compounds. Only simple substituents off of the piperazinyl group (the A substituents) are disclosed in Poulenc. Nowhere is the heterocycl-NH-C(=X)- substituent of the present invention of Formula (3a) disclosed or suggested in Poulenc, let alone the additional requirement of an oxo or thioxo substituent on the heterocycl. Further, there is nothing in the reference that teaches or suggests to modify the compounds of Poulenc to give the compounds of the present invention. Firstly, the chemistry is substantially different and it would not be expected by those of skill in the art to modify the Poulenc compounds in at least two ways in order to obtain the presently claimed compounds. Nor would it be obvious that such a (non-obvious) modification of compounds useful as antimalarials, anthelmintics and amoebicides (that is, activity against microbes) would give a substantially structurally different compound having CCR5 receptor antagonistic activity for treatment of inflammatory and autoimmune diseases in humans.

The claimed quinoline structure of the present invention is neither taught nor suggested in Rhone Poulenc. Thus, there is no suggestion whatever that the oxo- or thioxo-substituted heterocycl-NH-C(=X)- group of the invention should be substituted for the hydrocarbon groups (A) of Poulenc, and there is certainly no motivation to combine the teachings in Poulenc to get the heterocycl-NH-C(=X)- group since, in fact, Poulenc does not in any way teach such a group. Rhone Poulenc fails to set forth a necessary element, the heterocycl-NH-C(=X)- group, of the presently claimed invention. Therefore, the claims are not obvious in view of Rhone Poulenc, FR 84 902.

In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

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5. Claim 8-19 are rejected as being unpatentable over Agrawal et al., *Indian J of Chem* 1987. In particular, the Office Action states that

Agrawal teaches a generic group of quinoline derivatives, which embraces Applicants' claimed compounds. (See Abstract and formula 1, and pp. 550-555).... The claims differ from the reference by reciting specific species and a more limited genus than the reference. However, it would have been obvious ... to select any of the species of the genus taught by the reference, including those instantly claimed, because the skilled chemist would have the reasonable expectation that any of the species of the genus would have ... the same use as taught for the genus as a whole. [emphasis added]

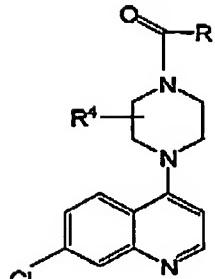
Response: Applicant respectfully traverses this rejection; the Examiner has not made out a case of *prima facie* obviousness.

As has been discussed more fully above, to properly support a rejection based upon *prima facie* obviousness, the Examiner must cite to a combination of prior art references or, as in the present case to a single reference that sets forth the necessary elements of the claimed invention *and* which provides the motivation for combining those elements to yield the claimed invention. The Federal Circuit has required that specific support must be found in the prior art that "suggests" or "teaches" the modification necessary to resolve the differences of the prior art with a claimed invention. If either the necessary elements of the invention or the motivation to combine such elements is missing, the Examiner cannot properly support the rejection based upon 35 USC §103 and it must be withdrawn.

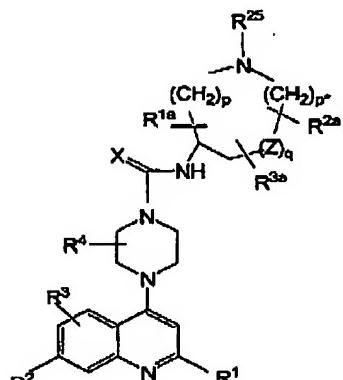
Applicant respectfully submits that the obviousness rejection is improper for two reasons. First, there is *no* suggestion or motivation in this one prior art reference to combine its teachings to carry out the claimed invention. Second, even if, *arguendo*, the reference could possibly be interpreted as suggesting the combination, the reference cited by the Examiner *fails* to set forth necessary elements of the claimed invention.

Contrary to the Office Action's statement, the quinoline derivatives of Agrawal do not embrace Applicants' claimed compounds. Only simple substituents off of the piperazinyl group are disclosed in Agrawal. The compounds of Agrawal closest to those of the present invention are on p.551 (reproduced below, where R is N(Et)₂, alkoxy, cycloalkyl, or haloalkyl):

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Agrawal et al.



Invention of formula (3a)

Nowhere is the heterocyclyl-NH-C(=X)- substituent of the present invention of Formula (3a) disclosed or suggested in Agrawal, let alone the additional requirement of an oxo or thioxo substituent on the heterocyclyl. Further, there is nothing in the reference that teaches or suggests to modify the compounds of Agrawal to give the compounds of the present invention. Firstly, the chemistry is substantially different and it would not be expected by those of skill in the art to modify the Agrawal compounds in at least two ways in order to obtain the presently claimed compounds. Nor would it be obvious that such a (non-obvious) modification of compounds useful as antiparasitic agents (that is, having activity against microbes) would give a substantially structurally different compound having CCR5 receptor antagonistic activity for treatment of inflammatory and autoimmune diseases in humans.

The claimed quinoline structure of the present invention is neither taught nor suggested in Agrawal. Thus, there is no suggestion whatever that the oxo- or thioxo-substituted heterocyclyl-NH-C(=X)- group of the invention should be substituted for the R groups of Agrawal, and there is certainly no motivation to combine the teachings in Agrawal to get the heterocyclyl-NH-C(=X)- group since, in fact, Agrawal does not in any way teach such a group. Agrawal fails to set forth a necessary element, the heterocyclyl-NH-C(=X)- group, of the presently claimed invention. Therefore, the claims are not obvious in view of the Agrawal reference.

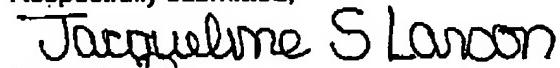
In view of the above remarks, Applicants respectfully request that the Examiner withdraw this §103(a) rejection.

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CONCLUSION

The Office Action dated 12/07/2006 has been carefully considered. It is believed that the amendments submitted herein and the above comments represent a complete response to the Examiner's rejections and place the present application in condition for allowance. Reconsideration is respectfully requested.

Respectfully submitted,


Jacqueline S. Larson
Patent Attorney for Applicants
Registration No. 30279Date: June 6, 2006

Berlex Pharmaceuticals
Corporate Patents
2600 Hilltop Drive
P.O. Box 4099
Richmond, California 94804-0099
Telephone: (510)-669-4483
Fax: (510)-262-7095
Email: jackie_larson@berlex.com